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TEMPERATURE-SENSITIVITY OF GABAA RECEPTOR TRAFFICKING IN A MOUSE MODEL OF FEBRILE SEIZURES

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Rationale: A substitution mutation in the $\gamma 2$ subunit of the GABAA receptor (R43Q) has been linked with Febrile Seizures (FS) in a large Australian family. The $\gamma 2$ subunit is integral in receptor trafficking and clustering at the synapse, without which, the efficacy of synaptic inhibition is severely impaired. While the precise mechanism underlying the generation of FS in the R43Q mutant has not been elucidated, a temperature-dependent trafficking deficiency in cell lines transfected with the R43Q mutation has been proposed to underlie FS susceptibility. Using a mouse model harbouring the same mutation, we test the hypothesis that temperature dependent receptor trafficking deficiency triggers FS, through the use of behavioural and EEG analysis, patch clamp electrophysiology, and radioligand binding.

Methods: Thermal seizure (TS) thresholds were assessed in P14–17 WT and heterozygous (RQ) mice during heating by hot air stream with concurrent measurement of rectal temperature. EEG recordings were obtained from epidural and depth electrodes in P18–23 mice. IPSCs were recorded from layer 2/3 pyramids in acute somatosensory cortical slices. Inhibitory currents were recorded using whole cell patch clamp, at 34°C following incubation at room temperature (RT) or 38°C (heated) for 1 hr. Whole brains from heated or non-heated P14 mice were obtained for a binding assay for the benzodiazepine ligand, [3H]flumazenil (FMZ) in order to investigate functional interactions between α and γ subunits. Heated animals were maintained at 40–41.5°C for 30 mins prior to tissue collection.

Results: R43Q animals show a reduced temperature threshold for TS compared to WT littermates. Depth electrode field potential recordings from the hippocampal region, but not cortical areas, showed slow (2–3 Hz) rhythmic spiking during TS. IPSCs recorded from RT and heated acute cortical slices did not show a temperature-dependent change in amplitude. At RT, R43Q current amplitudes were reduced compared to WT, while IPSC amplitudes from heated R43Q slices were increased in comparison with WT. Mean FMZ binding in homogenates from non heated animals is reduced in R43Q compared with WT. In mice subjected to thermal stress, FMZ binding was not significantly different from that seen in RT controls.

Conclusions: R43Q mice display reduced temperature threshold for TS recapitulating FS found in patients with the same mutation. The earlier proposal, in heterologous expression systems, of mutation specific temperature dependent increases in receptor trafficking are not recapitulated, by our current data from acute cortical slices and the FMZ binding. Altered hippocampal EEG characteristics with thermal stress are in agreement with earlier reports from rodent models suggesting the involvement of hippocampal activity in FS.